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ב ק ש ה ל פ ט נ ת
Application for Patent

אני, (שם המבקש, מענו ולגבי גוף מאגד - מקום התאגדות)
I, (Name and address of applicant, and in case of body corporate - place of incorporation)

ירום כהן

YAROM COHEN

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רמת אפעל 52960

ששמה הוא
of an invention the title of which is

הדין

בעל אמצאה מכח
Owner, by virtue of

PHARMACEUTICAL COMPOSITION

מבקש בזאת כי ינתן לי עליה פטנט.

hereby apply for a patent to be granted to me in respect thereof.

*דרישה דין קדימה Priority Claim		מדינת האגוד Convention Country	
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חתימת המבקש		היום 10 This of	
Signature of Applicant		בחודש of	
שנה 1996 of the year		אוקטבר	
For the applicant: DR. YITZHAK HESS & PARTNERS BY:		לשימוש הלשכה For Office Use	

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* Delete whatever is inapplicable - מחק את המיותר

תערבת רוקחות
PHARMACEUTICAL COMPOSITION

YAROM COHEN

The present application is an Application of Addition to Patent Application No. 119,250.

5 In Patent Application No. 119,250, there have been described pharmaceutical preparations for the treatment of the risk factors of Syndrome X of Reaven comprising as active ingredient Somatostatin or one of its analogs, as defined in said application.

10 It is known that Diazoxide, Cyclothiazide and Metformin achieve the reduction of the resistance to Insulin. Moreover, it is known that Metformin is used in the treatment of Diabetes and reduces risk factors in cardiovascular diseases in NIDDM. However, it has so far not been known to use said compounds in the treatment of the risk factors of syndrome X of Reaven.

It has now been found that said compounds can be used for the treatment of the risk factors of syndrome X of Reaven.

15 The present invention thus consists in pharmaceutical preparations for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among diazoxide or one of its analogs (as herein defined); cyclothiazide or one of its analogs (as herein defined); and metformin.

The above compounds have the following formulae:

- 25
- a. Diazoxide: 7-chloro-3-methyl-24-1,2,4-benzothio-diazine 1,1-dioxide.
 - b. Cyclothiazide: 3-bicyclo[2.2.1]hept-5-en-2yl-6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
 - c. Metformin: N,N-Dimethylimidodicarbonimide diamide.

Analogs of Diazoxide and Cyclothiazide are compounds which affect the receptor being adenosine 5'- triphosphate sensitive K⁺ channels.

30 Suitable analogs of Diazoxide and of Cyclothiazide are

indicated, for example, in a paper of Bertolino et al., appearing in Receptor-Channels 1993 1(4):267-78 "Modulation of AMPA/Kainate Receptors by Analogs of diazoxide and cyclothiazide in thin slices of rat hippocampus". However, the analogs which may be used in the pharmaceutical composition according to the present invention are not restricted to the analogs given in said paper and any other analog having the proper properties may be used.

The pharmaceutical preparations according to the present invention may also comprise additional compounds, such as compounds having an additional pharmaceutical effect, carriers, solvents, amalgamators, etc.

In view of the fact that diazoxide sometimes has undesired salt and water retention, which may be relieved by certain thiazide diuretics, e.g. 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Chlorothiazide); 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Hydrochlorthiazide); 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Trichlormethiazide); or 6-chloro-3,4-dihydro-2-methyl-3[(2,2,2-trifluoroethyl)thiomethyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Polythiazide), the pharmaceutical compositions according to the present invention may comprise, in addition to Diazoxide and/or one of its analogs, as an additional compound having a pharmaceutical effect, one or more of the above thiazides or a thiazide having similar properties. Said thiazide diuretics may prevent the salt and water retention.

The active ingredient and the additional compound may be part of the same preparation or given separately.

The present invention also consists in a method for the treatment of the risk factors of syndrome X of Raven by applying to a patient a pharmaceutically effective dosage of the above

pharmaceutical preparations.

Said dosage is given in any suitable manner. Said dosage has to be re-calculated on the basis of the active ingredient being comprised in the pharmaceutical composition. Moreover, the exact dosage has to be adapted to the condition of the patient and to his specific properties, i.e. weight, age, etc.

Said dosage should preferably not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and preferably not exceed 15/mg/day in the treatment of children. The amount of Metformin applied should preferably not exceed 2.5 g/day divided into 2 - 3 portions.

Should any of the above thiazide diuretics be added the added amounts are, for example, the following:

Chlorothiazide: 500 - 2000 mg a day;

Hydrochlorothiazide: 50 - 200 mg a day;

Trichloromethiazide: 12.5 - 50 mg a day;

Polythiazide: 1- 4 mg a day.

The above compounds and/or compositions are advantageously administered per-os.

Claims

1. Pharmaceutical preparations for the treatment of the risk factors of syndrome X of Raven comprising as active ingredient a compound selected among diazoxide or one of its analogs (as herein defined); cyclothiazide or one of its analogs (as herein defined); and metformin.
2. Pharmaceutical preparations according to Claim 1 which comprise additional compounds, such as compounds having an additional pharmaceutical effect, carriers, solvents, amalgamators, etc.
3. Pharmaceutical preparations according to Claim 2, wherein the additional compound is selected among Chlorothiazide, Hydrochlorothiazide, Trichlorothiazide and Polythiazide.
4. A method for the treatment of the risk factors of syndrome X of Reaven by applying to a patient a pharmaceutically effective dosage of the pharmaceutical preparations according to any of Claims 1 to 3.

For the Applicant:

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By: 

